REMARKS

Claims 8 and 10-18 are pending in the application.

Rejections under 35 U.S.C.§103

In the Office Action, the Examiner maintains the rejection of the claims over Kondo, combined with Harada, and Shirakawa. The Examiner also raises a new prior art rejection of claims 8 and 10-16 over Kondo, combined with Harada, Shirakawa, and the newly cited references of Galle, Dienes and Luo. These rejections are addressed in turn below.

1) *Kondo, combined with Harada, and Shirakawa* - On pages 3-7 of the Office Action the Examiner details why she finds Applicants' arguments insufficient to overcome the rejection. Applicants will address each point raised by the Examiner.

a) The Examiner maintains that the only important aspect of Graham et al. is that PBC cells express Fas/CD95. The Examiner refuses to find the teachings of Graham et al. and Harada et al. as inconsistent. The Mirriam-Webster Online Dictionary defines "inconsistent" as "not compatible with another fact or claim." Harada et al. claim that CD95/Fas is up-regulated, i.e. increased, in PBC. Graham et al., on the other hand, claim that there is no change in Fas with PBC. The fact remains that these two claims offered by these separate articles are inconsistent with each other. It is inconsistent to say that something is both changing

and staying the same. Thus, contrary to the assertion of the Examiner the findings of Graham et al. and Harada et al. are inconsistent and indicative of the unpredictability of the art at the time of the invention.

b) Regarding Applicants' arguments that the Leithäuser et al. (1993) and Hiramatsu et al. (1994) are indicative of the state of the art, the Examiner responds that the references having a publication date closer to that of the invention are more probabative of the state of the art.

Generally speaking, the Examiner may be correct and references published later would be presumptively more indicative of the state of the art. However, Applicants have overcome and rebutted this presumption in the present situation by the showing that the earlier published references are cited as being the accepted state of the art in references contemporary with the invention. Thus, even though Leithäuser et al. (1993) and Hiramatsu et al. (1994) predate the references relied on by the Examiner, both Leithäuser et al. (1993) and Hiramatsu et al. (1994) are still evidentiary of the accepted teachings at the time of the invention.

c) The Examiner states, that "It is well established in the art that chronic hepatitis leads to hepatic cirrhosis, therefore a method that will prevent the inflammation and destruction of liver

cells (hepatocytes) will prevent the occurrence of hepatic cirrhosis." In this regard, the Examiner appears to have ignored the comments of pages 6-8 of the March 15, 2004 response. As discussed previously, Harada et al. do teach that Fas expression and TUNEL index were high on pathological tissues. However, Harada et al. does not actually look at whether apoptosis mediated by Fas is involved in the pathology. The involvement of Fas is only a hypothesis that Harada et al. offer based on their results. See page 1404, lines 21-12 from the bottom.

However, the conclusion reached by Harada et al. was in opposite to that of Graham et al. wherein it was concluded that apoptosis is unlikely to be a suitable therapeutic target for treating PBC. See the final sentence of page 556. Graham et al. further stated that while it had been reported that apoptosis may be induced on pathological tissues, but that it was unlikely that the mechanism involved was Fas-mediated. See page 556, lines 6-8.

Thus, a full consideration of the overall state of the art, clearly shows that the involvement of Fas-mediated apoptosis in the pathology was highly controversial at the time of the invention.

Concomitant with the inconsistent findings in the art at the time of the invention, Takiya et al. (1995) discussed on page 6 of the January 15, 2004 response supports that the expression of Fas does not correspond to TUNEL activity. Similarly, Ballardini et

al., *Dig. Liver Dis.* 33:151-156 (2001), support that increased Fas expression does not necessarily lead to apoptosis.

Thus, contrary to the conclusion of the Examiner, one skilled in the art would have no expectation of success or be motivated to achieve the invention from the teachings of the prior art.

d) On page 5 of the Office Action, the Examiner again takes the position that the arguments previously submitted are arguments of counsel, which are not supported by evidence. The Examiner further states, "Applicants base their argument that low level of expression would prevent apoptosis from being mediated through the CD95/Fas pathway." However, the Examiner completely ignores the fact that the statement regarding a low level of expression was, in fact, made in the Graham et al. reference, not by Applicants. The Examiner is again directed to some of the relevant citations in Graham et al., for example, page 556, column 2, lines 4-6 and page 556, final sentence. More importantly, this citation to Graham et al. was made in support of the argument that the art had contradicting reports and therefore was not predictable. Applicants have never taken the position that the "Fas pathway is not powerful". Applicants have taken direct quotations from the references, i.e. not opinions of counsel, to establish that the state of the art was unpredictable at the time of the invention.

e) On page 6, the Examiner asserts that there is no teaching in Graham et al., which suggests that CD95/Fas is not present on primary biliary epithelial cells. Applicants again note that Graham et al. is relied upon by Applicants to establish that at the time of the invention the state of the art was unpredictable. As noted above, Graham et al. state that Fas expression is unchanged in PBC, Harada et al. state that Fas expression increased in PBC. Again, something cannot be both staying the same and changing and the findings and conclusions in the state of the art were therefore inconsistent and unpredictable at the time of the invention.

2) *Kondo, combined with Harada, Shirakawa and the newly cited references of Galle, Dienes and Luo*

Galle et al. is relied on for teaching the absence of Fas RNA in normal liver but the presence of Fas RNA in damaged liver. Galle et al. is further asserted to teach that anti-Fas antibodies induce apoptic cell death of primary hepatocytes. Dienes et al. is asserted to teach bile duct epithelial cells in primary biliary cirrhosis express Fas. Luo et al. is asserted to teach the up regulation of Fas in hepatocytes with hepatitis.

The Examiner relies on the new references for the overall teachings of the presence of Fas in primary biliary cirrhosis. The Examiner further asserts that since bile duct disappearance is cased by primary biliary cirrhosis, the same mechanism would be involved with both pathologies. However, the newly cited

references are cumulative with the earlier cited references and have the same failure of the other references of showing a direct involvement of Fas-mediated apoptosis in the progression of the disease states.

At the time of the invention it was completely unknown with the pathology of primary biliary cirrhosis (PBC), whether Fas-mediated apoptosis makes the pathology better or worse, when Fas ligand binds to Fas on biliary epithelial cells.

For example, it was possible that when Fas ligand and Fas interact on biliary epithelial cells, which are responsible for PBC, Fas-mediated apoptosis might be induced to replace the diseased cells with normal cells, thus improving the disease state. Indeed, if the role of Fas/Fas ligand in other pathologies is considered, one skilled in the art would conclude that it would more likely be desirable to treat PBC-related pathologies by inducing apoptosis. For example, WO 95/32627 teaches that Fas agonists (in this case Fas ligand) are useful in treating transplantation rejection, diabetes, rheumatoid arthritis (RA), multiple sclerosis, cystic fibrosis etc. EP 0709097 similarly teaches that Fas agonists (in this case anti-Fas antibody) are useful for treating rheumatoid disorders, such as RA.

Thus, at the time of the invention, it was not known whether it was more desirable to inhibit Fas-mediated apoptosis (with a Fas antagonist) or to induce Fas-mediated apoptosis (with a Fas

agonist). The present invention for the first time, has considered this issue directly and has for the first time achieved a method of treating hepatic cirrhosis or bile duct disappearance syndrome by inhibiting Fas-mediated apoptosis (claim 8). Thus, the present invention is not obvious over cited references of the Examiner and withdrawal of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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